A “Catch-React-Release” method for the flow synthesis of 2-aminopyrimidines and preparation of the imatinib base¹

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Background

2-Aminopyrimidines are key heterocyclic components of compounds with diverse pharmacologies, including antiemetic,² antitumour,³ antiinflammatory⁴ and antimalarial⁵ activity. A well-known example is the tyrosine kinase inhibitor imatinib, marketed by Novartis as its mesylate salt, Gleevec.

The aminopyrimidine moiety is often formed via metal-

catalysed cross coupling at the guanidine centre (Scheme 1).^{5,6} However, we considered an alternative method involving the displacement of a thiol (Scheme 2)^{7,8} to be more powerful, particularly considering the potential for late-stage diversification. However, this method is not well represented in the literature, possibly because the key displacement step involves the release of thiol by-products, which are malodorous and often

toxic — making this process undesirable to perform.

Building on our group's experience with polymer-supported reagents,⁹ we envisaged that by performing this reaction with the sulfur tethered to a solid support (Scheme 3), no thiol byproducts would be released, making this reaction more palatable in a research laboratory environment.

We have developed a solid-phase synthesis of these important precursors, reviving some of the positive aspects of the combinatorial chemistry era. This procedure circumvents potential problems from poor solubility of the intermediates, found to be a challenge in alternate routes.¹⁰ We applied our flow technology to perform a machine-assisted synthesis of these compounds.

Solid Reagent Synthesis

Machine Control

A number of the steps involved long periods of time to wait between changing the parameters of the flow platform on which the syntheses were performed. Fortunately, these devices have been designed to operate semi-autonomously, allowing the chemist to spend this time more productively.

We implemented an interface to the Vapourtec R2+/R4 flow synthesis platform using the Python programming language, to allow the machine to perform a custom sequence of operations, mostly unattended. Work is ongoing to implement safety tools such as SMS notifications if the machine reports a problem.

```
r = vapourtec.R2R4(tcp("192.168.15.151", 9001))

r.temp(1, 80)
r.output("waste")
r.flowrate("both", 100)
r.input("both", "reagent")
wait("3h30m")

r.temp(1, 25)
r.input("both", "solvent")
wait("30m")

r.off()

r.output("waste")
r.flowrate("orange", 100)
r.input("orange", "reagent")
wait("3h30m")

r.input("orange", "solvent")
wait("30m")

r.off()

r.temp(1, 80)
r.output("collect")
r.input("both", "reagent")

for i in range(4)
    r.flowrate("both", 100)
    wait("30m")
    r.flowrate("both", 0)
    wait("2h")

r.temp(1, 25)
r.input("both", "solvent")
wait("30m")

r.off()
```

Monolithic Reagents

Compared to the gel-phase beads traditionally associated with solid-supported chemistry, solid reagents generated as monoliths boast a number of advantages:

Cross-linked polymer structure

- Is structurally very rigid.
- Fills the column completely.
- Does not swell or shrink in different solvents.

Polymer beads in a "poor" solvent shrink, and reagent stream can channel around.

Polymer beads in a "good" solvent swell, and reagent stream can be blocked.

High porosity

- Large surface area.
- Reaction rates are not limited by diffusion into the solid reagent.
- Pore sizes are tunable by altering the polymerisation mixture.

Close-ups of monolith structure, as observed by a scanning electron microscope

Easy to manufacture

- No special equipment is required.
- Challenging substrates can be incorporated.

Heterocycle Synthesis

2-Aminopyrimidine Products

A collection of ten 2-aminopyrimidine heterocycles were produced in a high degree of purity, each requiring only a single purification operation by column chromatography.

Vapourtec R2+/R4 flow synthesis platform

References and Acknowledgements

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